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=> D HIS FULL

     (FILE 'HOME' ENTERED AT 10:29:29 ON 21 APR 1999)
CHARGED TO COST=09.187,763

     FILE 'REGISTRY' ENTERED AT 10:29:47 ON 21 APR 1999
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L1              STRUCTURE UPLOADED
L2            0 SEA SSS SAM L1
L3            9 SEA SSS FUL L1

     FILE 'BEILSTEIN' ENTERED AT 10:30:40 ON 21 APR 1999
CHARGED TO COST=09.187,763
L4            0 SEA SSS FUL L1

     FILE 'MARPAT, MARPATPREV' ENTERED AT 10:31:01 ON 21 APR 1999
CHARGED TO COST=09.187,763
L5            1 SEA L3

     FILE 'CAPLUS' ENTERED AT 10:31:58 ON 21 APR 1999
CHARGED TO COST=09.187,763
L6            7 SEA L3

     FILE 'CAPLUS, MARPAT' ENTERED AT 10:32:26 ON 21 APR 1999
CHARGED TO COST=09.187,763
L7            7 DUP REM L6 L5 (1 DUPLICATE REMOVED)


     FILE HOME

     FILE REGISTRY
     STRUCTURE FILE UPDATES:  16 APR  99  HIGHEST RN 221295-00-7
     DICTIONARY FILE UPDATES: 21 APR  99  HIGHEST RN 221295-00-7

     TSCA INFORMATION NOW CURRENT THROUGH JANUARY 13, 1999

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

     FILE BEILSTEIN
     FILE LAST UPDATED: 1 MAR 1999

     FILE COVERS 1779 TO 1999.
      CAS REGISTRY NUMBERS FOR 4,356,237 SUBSTANCES AVAILABLE
      FILE CONTAINS 7,446,355 SUBSTANCES

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     * PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST.      *
     * SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE  *
     * ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE *
     * ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS.              *
     * FOR PRICE INFORMATION SEE HELP COST                      *
     ************************************************************


     FILE MARPAT
     FILE CONTENT: 1988-PRESENT (VOL 108 ISS 12-VOL 130 ISS 15)(19990416/ED)

     MOST RECENT CITATIONS FOR PATENTS FROM FIVE MAJOR ISSUING AGENCIES
```

(COVERAGE TO THESE DATES IS NOT COMPLETE):

US 5882934 16 MAR 1999
DE 19834152 18 MAR 1999
EP 903398 24 MAR 1999
JP 11065107 05 MAR 1999
WO 9913691 18 MAR 1999

MARPAT structure search limits have been raised.
Enter HELP SLIMIT for details.

FILE MARPATPREV
FILE COVERS CURRENT RECORDS AND IS UPDATED DAILY
FILE LAST UPDATED: 21 APR 1999 (19990421/ED)

MOST RECENT CITATIONS FOR PATENTS FROM FIVE MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):
US 5882934 16 MAR 1999
DE 19834152 18 MAR 1999
EP 903398 31 MAR 1999
JP 11071146 16 MAR 1999
WO 9915508 01 APR 1999

MARPATprev structure search limits have been raised.
Enter HELP SLIMIT for details.

FILE CAPLUS

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FILE COVERS 1967 - 21 Apr 1999 VOL 130 ISS 17
FILE LAST UPDATED: 21 Apr 1999 (19990421/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> D IBIB IABS HITSTR TOTAL

L7 ANSWER 1 OF 7 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 1
ACCESSION NUMBER: 1999:96249 CAPLUS
DOCUMENT NUMBER: 130:158419
TITLE: Antiviral nucleotide analog composition and synthesis method
INVENTOR(S): Munger, John D., Jr.; Rohloff, John C.; Schultze, Lisa M.
PATENT ASSIGNEE(S): Gilead Sciences, Inc., USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9905150	A1	19990204	WO 98-US15254	19980723

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 97-53777 19970725
US 97-900752 19970725

OTHER SOURCE(S): MARPAT 130:158419

ABSTRACT:
The invention provides a compn. comprising 9-[2-(R)-[[Bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]adenine [bis(POC)PMPA] and fumaric acid (1:1) for oral delivery of (R)-9-[2-(phosphonomethoxy)propyl]adenine (PMPA). The compn. is useful as an intermediate for the prepn. of antiviral compds., or is useful for administration to patients for antiviral therapy or prophylaxis. The compn. is particularly useful when administered orally. The invention also provides methods to make PMPA and intermediates in PMPA synthesis. Embodiments include lithium t-butoxide, 9-(2-hydroxypropyl)adenine and di-Et p-toluenesulfonylmethoxy-phosphonate in an org. solvent such as DMF. The reaction results in di-Et PMPA prepns. contg. an improved byproduct profile compared to di-Et PMPA made by prior methods. "Bis(POC)PMPA" fumarate, or BPPF, was prepd. in 7 steps via reaction of (R)-4-methyl-1,3-dioxolan-2-one with adenine and etherification of the product with (EtO)2P(O)CH2-OTs.

IT **202138-50-9P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of (phosphonomethoxypropyl)adenine analogs for oral drug delivery)

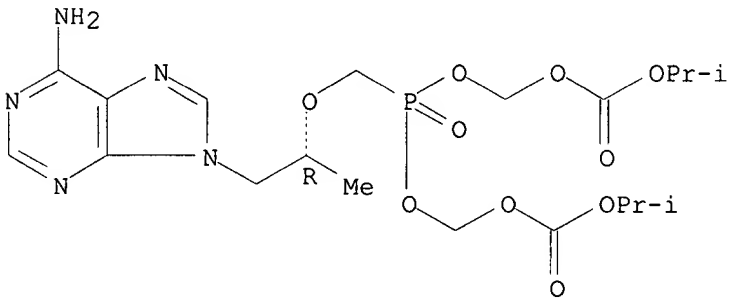
RN 202138-50-9 CAPLUS

CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 201341-05-1
CMF C19 H30 N5 O10 P

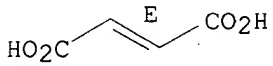
Absolute stereochemistry.



CM 2

CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

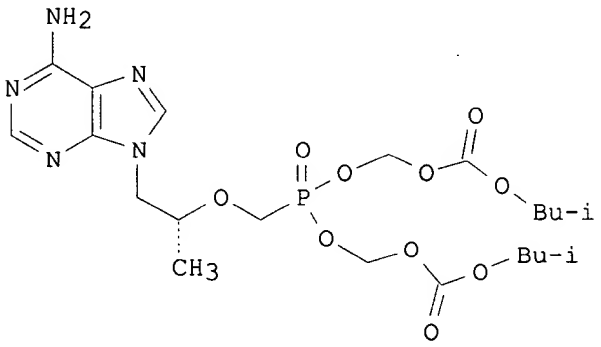
Double bond geometry as shown.



L7 ANSWER 2 OF 7 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:102883 CAPLUS
DOCUMENT NUMBER: 128:140970
TITLE: Preparation of phosphonomethoxy acyclic nucleotide analogs as antiviral agents
INVENTOR(S): Arimilli, Murty N.; Cundy, Kenneth C.; Dougherty, Joseph P.; Kim, Choung U.; Oliyai, Reza; Stella, Valentino J.
PATENT ASSIGNEE(S): Gilead Sciences, Inc., USA
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9804569	A1	19980205	WO 97-US13244	19970725
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9738970	A1	19980220	AU 97-38970	19970725
PRIORITY APPLN. INFO.:			US 96-22708	19960726
			US 96-686838	19960726
			WO 97-US13244	19970725

OTHER SOURCE(S): MARPAT 128:140970
GRAPHIC IMAGE:

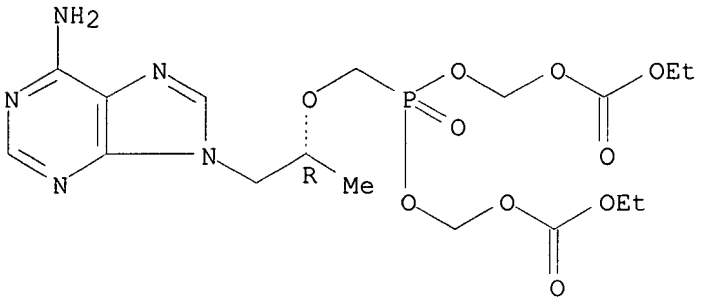


I

ABSTRACT:
Compds. are provided that comprise esters of antiviral phosphonomethoxy nucleotide analogs with carbonates and/or carbamates having the structure B-OC(R2)2OC(O)X(R)n, wherein R2 independently is H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro or OR3 in which R3 is C1-C12 alkyl; X is N or O; R is independently H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro, -O-, -N=, -NR4, -N(R4)2- or OR3, R4 independently is -H or C1-C8 alkyl, provided that at least one R is not H; and n is 1 or 2, with the proviso that when n is 2 and X is N, (a) two R groups can be taken together to form a carbocycle or oxygen-contg. heterocycle, or (b) one R addnl. can be OR3. The compds. are useful as intermediates for the prepn. of antiviral compds. or oligonucleotides, or are useful for administration directly to patients for antiviral therapy or prophylaxis. Embodiments are particularly useful when administered orally. Thus , acyclic nucleotide I was prepd. and showed anti-HIV activity (IC50 < 0.001 .mu.M).

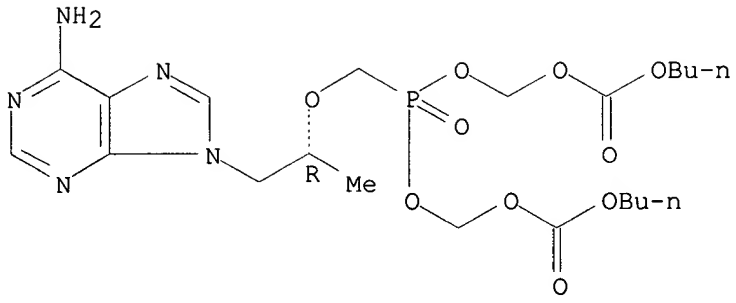
IT **201340-95-6P**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of phosphonomethoxy acyclic nucleotide analogs as antiviral agents)
RN 201340-95-6 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, diethyl ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



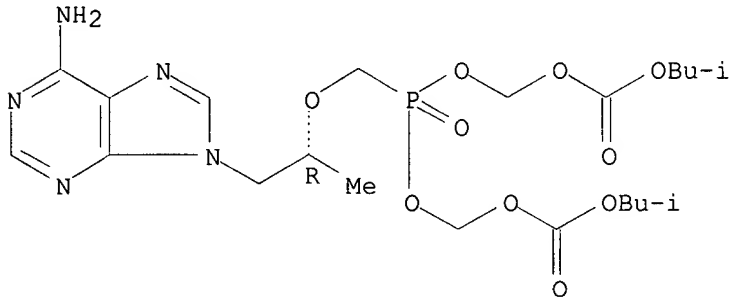
IT **201340-97-8P 201340-99-0P 201341-01-7P**
201341-03-9P 201341-05-1P 201341-07-3P
202138-50-9P 202138-51-0P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of phosphonomethoxy acyclic nucleotide analogs as antiviral agents)
RN 201340-97-8 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, dibutyl ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



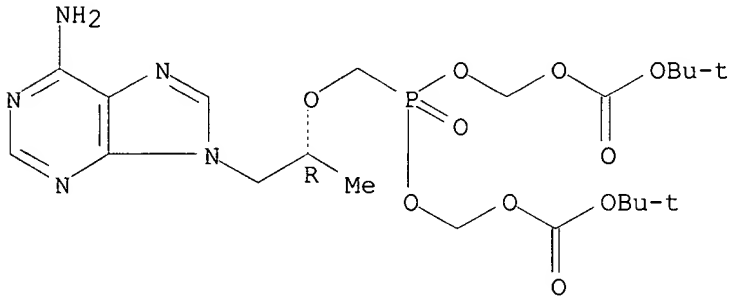
RN 201340-99-0 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(2-methylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



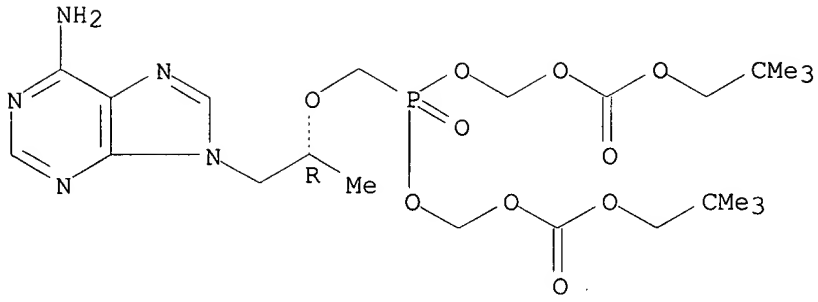
RN 201341-01-7 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1,1-dimethylethyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



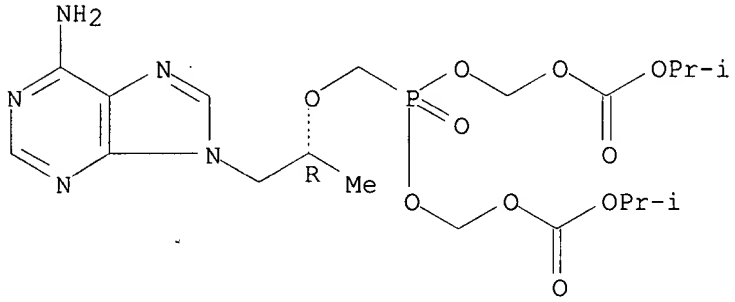
RN 201341-03-9 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(2,2-dimethylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



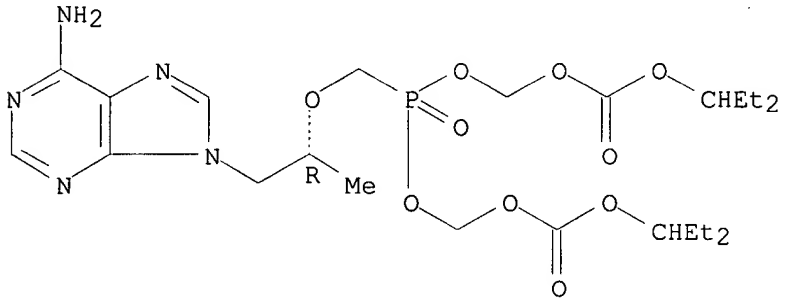
RN 201341-05-1 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 201341-07-3 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-ethylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



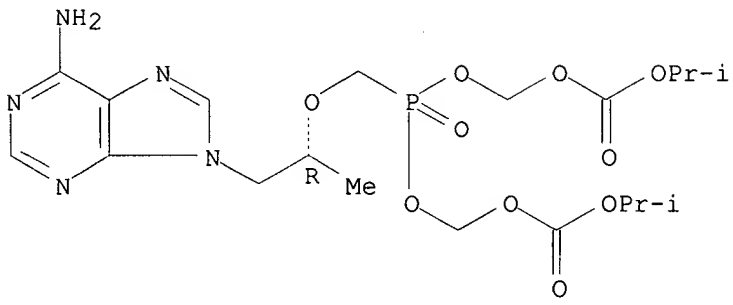
RN 202138-50-9 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 201341-05-1

CMF C19 H30 N5 O10 P

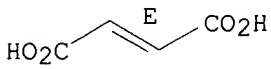
Absolute stereochemistry.



CM 2

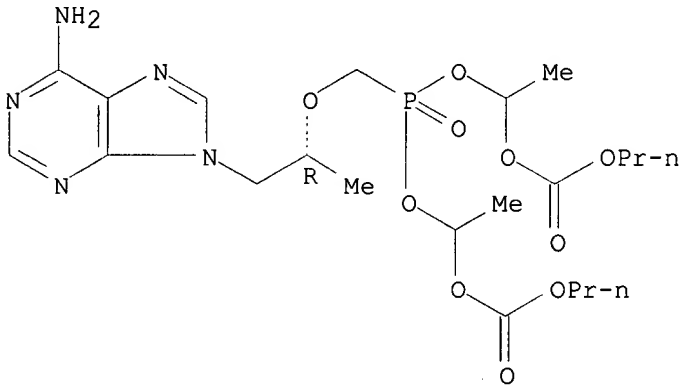
CRN 110-17-8
CMF C4 H4 O4
CDES 2:E

Double bond geometry as shown.



RN 202138-51-0 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-3,7-dimethyl-, dipropyl ester, 5-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

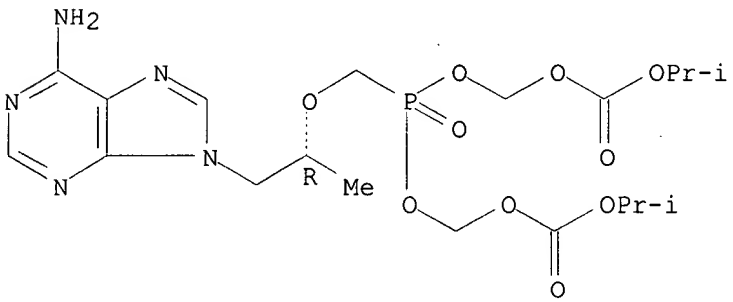


L7 ANSWER 3 OF 7 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:436276 CAPLUS
DOCUMENT NUMBER: 129:170075
TITLE: Antiretroviral efficacy and pharmacokinetics of oral bis(isopropyloxycarbonyloxymethyl)-9-(2-phosphonylmethoxypropyl)adenine in mice
AUTHOR(S): Naesens, Lieve; Bischofberger, Norbert; Augustijns,

Patrick; Annaert, Pieter; Van Den Mooter, Guy; Arimilli, Murty N.; Kim, Choung U.; De Clercq, Erik
CORPORATE SOURCE: Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: Antimicrob. Agents Chemother. (1998), 42(7), 1568-1673
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
ABSTRACT:
To overcome the low oral bioavailability of the highly potent and selective antiretroviral agent (R)-9-(2-phosphonylmethoxypropyl)adenine (PMPA), its lipophilic ester deriv. bis(isopropyloxycarbonyloxymethyl)-ester [bis(POC)-PMPA] was prepd. The usefulness of bis(POC)-PMPA as an oral prodrug for PMPA was investigated in the intestinal mucosa Caco-2 cell monolayer model. The total transport of bis(POC)-PMPA was 2.7%, whereas it was <0.1% for PMPA. Bis(POC)-PMPA was considerably metabolized inside the epithelial cells, since the majority of the compd. was recovered after transport in the form of the monoester metabolite mono(POC)-PMPA. Bis(POC)-PMPA was relatively resistant to degrdn. at the luminal side of the Caco-2 cells. Pharmacokinetic studies in mice showed that the oral bioavailability of bis(POC)-PMPA calcd. from the curves of the concn. of free PMPA in blood plasma was 20%. Neither bis(POC)-PMPA nor mono(POC)-PMPA could be recovered from blood plasma, suggesting the efficient release of the active drug PMPA after oral administration of bis(POC)-PMPA. Severe combined immunodeficient (SCID) mice infected with Moloney murine sarcoma virus (MSV) and treated orally with bis(POC)-PMPA for 5 or 10 days at dosages of 50, 100, or 200 mg PMPA equiv./kg/day showed a significant delay in MSV-induced tumor appearance and tumor-assocd. death. The antiviral efficacy of oral bis(POC)-PMPA was related to the dosage and treatment period and was not significantly different from that of s.c. PMPA given at equiv. doses. The favorable pharmacokinetic profile, marked antiviral efficacy, and low toxicity make bis(POC)-PMPA an attractive oral prodrug of PMPA that should be pursued in clin. studies in patients infected with human immunodeficiency virus or hepatitis B virus.

IT **201341-05-1**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(antiretroviral efficacy and pharmacokinetics of oral bis(isopropyloxycarbonyloxymethyl)-9-(2-phosphonylmethoxypropyl)adenine in mice)
RN 201341-05-1 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide (9CI) (CA INDEX NAME)

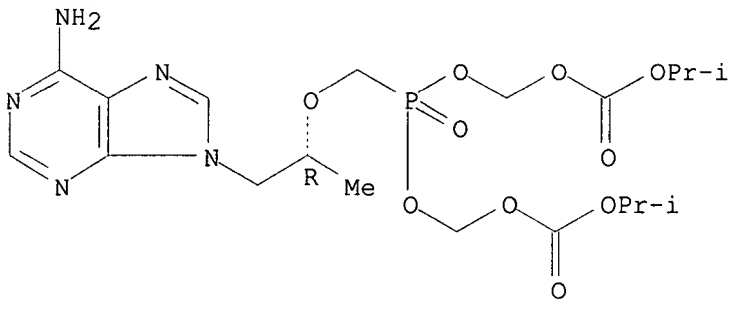
Absolute stereochemistry.



L7 ANSWER 4 OF 7 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:368901 CAPLUS
DOCUMENT NUMBER: 129:117461
TITLE: Antiviral activities of 9-R-2-phosphonomethoxypropyl adenine (PMPA) and bis(isopropyloxymethylcarbonyl)PMPA against various drug-resistant human immunodeficiency virus strains
AUTHOR(S): Srinivas, Ranga V.; Fridland, Arnold
CORPORATE SOURCE: Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SOURCE: Antimicrob. Agents Chemother. (1998), 42(6), 1484-1487
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
ABSTRACT:
9-R-2-Phosphonomethoxypropyl adenine (PMPA) is an acyclic nucleoside phosphonate analog with efficacy against human immunodeficiency virus (HIV). We recently described the synthesis, metab., and biol. activities of bis(isopropyloxymethylcarbonyl)PMPA [bis(poc)PMPA] as an orally bioavailable prodrug for PMPA. Among a large panel of drug-resistant HIV type 1 variants, only the K65R virus was resistant to PMPA. The K65R virus also showed reduced susceptibility to bis(poc)PMPA, although the prodrug could still inhibit these viruses at nontoxic submicromolar concns. In a panel of 7 primary clin. isolates from patients with diverse treatment histories, only one isolate showed reduced susceptibility to PMPA and was found to carry 3 mutations (M41L, T69N, R73K) in its reverse transcriptase catalytic domain.

IT **201341-05-1**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(HIV virus drug-resistant strains sensitivity to 9-R-2-phosphonomethoxypropyladenine (PMPA) and its precursor bis(isopropyloxymethylcarbonyl)PMPA)
RN 201341-05-1 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 5 OF 7 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:189766 CAPLUS
DOCUMENT NUMBER: 128:303669
TITLE: Anti-human immunodeficiency virus activity and cellular metabolism of a potential prodrug of the

acyclic nucleoside phosphonate 9-R-(2-phosphonomethoxypropyl)adenine (PMPA), bis(isopropyloxymethylcarbonyl)PMPA

AUTHOR(S): Robbins, Brian L.; Srinivas, Ranga V.; Kim, Choung; Bischofberger, Norbert; Fridland, Arnold

CORPORATE SOURCE: Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA

SOURCE: Antimicrob. Agents Chemother. (1998), 42(3), 612-617
CODEN: AMACCQ; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ABSTRACT:

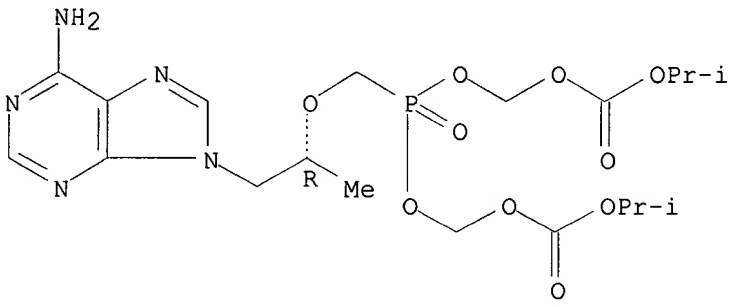
Bis(isopropyloxymethylcarbonyl) 9-R-(2-phosphonomethoxypropyl)adenine [bis(POC)PMPA] has been identified as a novel prodrug of PMPA. The anti-human immunodeficiency virus activity of bis(POC)PMPA was >100-fold greater than that of PMPA in both an established T-cell line and primary peripheral blood lymphocytes. This improved efficacy was shown to be due to a rapid intracellular uptake of the prodrug resulting in an increased intracellular accumulation of PMPA diphosphate (PMPApp), the pharmacol. active metabolite. PMPApp levels in bis(POC)PMPA-treated cells exceeded by >1000-fold the levels seen in cells treated with unmodified PMPA in both resting and activated peripheral blood lymphocytes. Significant differences in the intracellular catabolism of PMPA metabolites were noted between the resting and activated lymphocytes. The half-life for the disappearance of PMPApp, derived from either bis(POC)PMPA or PMPA, was 12 to 15 h in the activated lymphocytes and 33 to 50 h in the resting lymphocytes. This long persistence of PMPApp, particularly in resting lymphocytes, may be unique to the nucleoside phosphonate analogs and indicates that effective levels of the active metabolite can be achieved and maintained with relatively infrequent administration of the parent drug.

IT **201341-05-1**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(anti-HIV activity and cellular metab. of prodrug of (phosphonomethoxypropyl)adenine)

RN 201341-05-1 CAPLUS

CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 6 OF 7 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:41625 CAPLUS

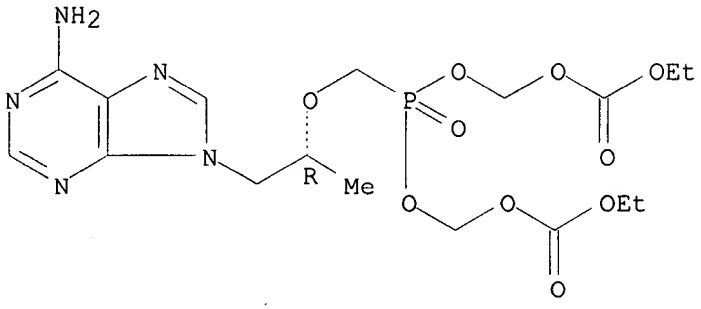
DOCUMENT NUMBER: 128:196530
TITLE: Metabolism and pharmacokinetics of novel oral prodrugs of 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) in dogs
AUTHOR(S): Shaw, Jeng-Pyng; Sueoka, Cathy M.; Oliyai, Reza; Lee, William A.; Arimilli, Murty N.; Kim, Choung U.; Cundy, Kenneth C.
CORPORATE SOURCE: Gilead Sciences, Inc., Foster City, CA, 94404, USA
SOURCE: Pharm. Res. (1997), 14(12), 1824-1829
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Plenum Publishing Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English
ABSTRACT:

A series of prodrugs designed to enhance the oral bioavailability of the antiretroviral agent 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) have been synthesized, including a bis-(acyloxymethyl) ester and a series of bis-(alkoxycarbonyloxymethyl) esters. All prodrugs were rapidly hydrolyzed in dog plasma and tissues (t1/2 <60 min). In fasted beagle dogs, bis[(pivaloyloxy)methyl] PMPA (bis-POM PMPA) had the highest oral bioavailability as PMPA (37.8 .+-. 5.1%). The oral bioavailabilities of PMPA from bis(alkoxycarbonyloxymethyl) esters ranged from 16.0% to 30.7% and PMPA was the major metabolite formed. There was a correlation between oral bioavailability and intestinal stability of bis(alkoxycarbonyloxymethyl) ester prodrugs (r2 = 0.96). Lipophilicity (log P) was not a good predictor of oral bioavailability. The most labile prodrugs in dog intestinal homogenates, bis(n-butyloxycarbonyloxymethyl) PMPA and bis-(neopentyloxycarbonyloxymethyl) PMPA (t1/2 <5 min) had the lowest oral bioavailabilities. Based on good oral bioavailability (30.1%), chem. and intestinal stability bis(isopropyloxycarbonyloxymethyl) PMPA (bis-POC PMPA) was selected as a candidate for clin. evaluation.

IT **201340-95-6 201340-97-8 201340-99-0**
201341-01-7 201341-03-9 201341-05-1
201341-07-3
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(metab. and pharmacokinetics of oral prodrugs of 9-[(R)-2-(phosphonomethoxy)propyl]adenine in dogs)

RN 201340-95-6 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, diethyl ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

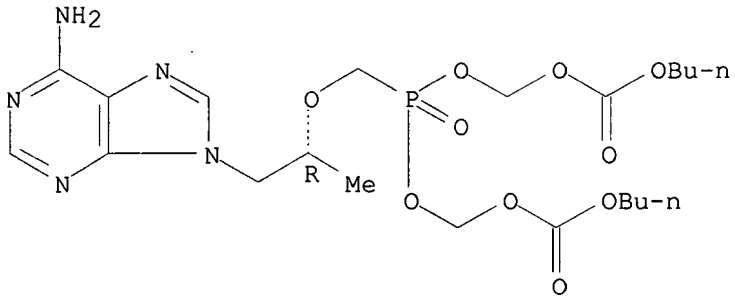
Absolute stereochemistry.



RN 201340-97-8 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-

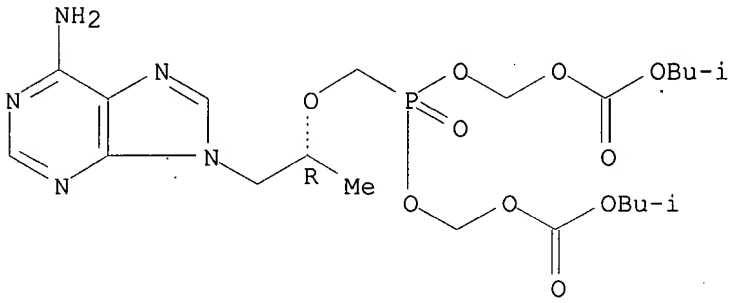
1-methylethoxy]methyl]-, dibutyl ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



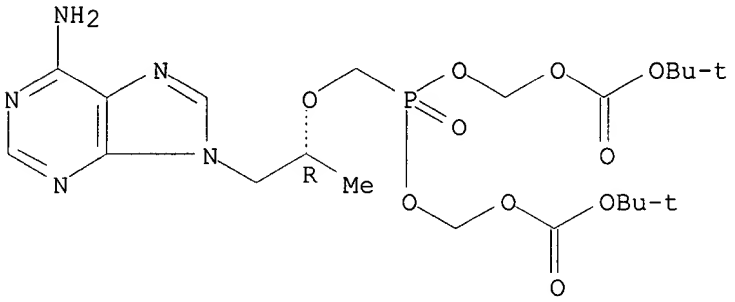
RN 201340-99-0 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(2-methylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 201341-01-7 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1,1-dimethylethyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

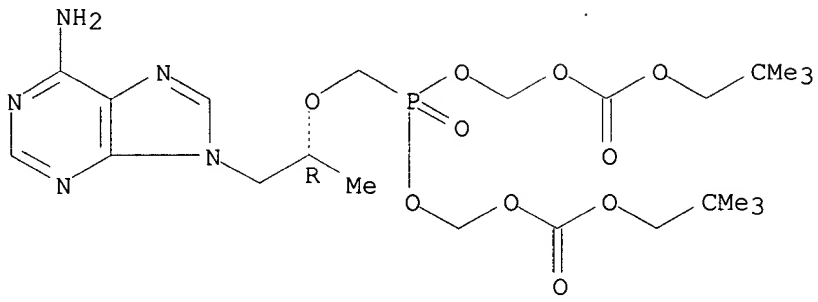
Absolute stereochemistry.



RN 201341-03-9 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(2,2-dimethylpropyl) ester, 5-oxide, (R)-

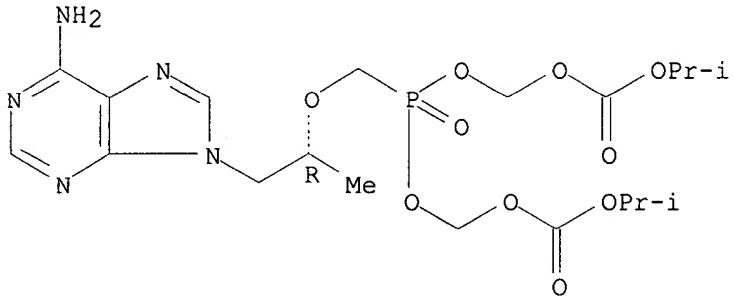
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



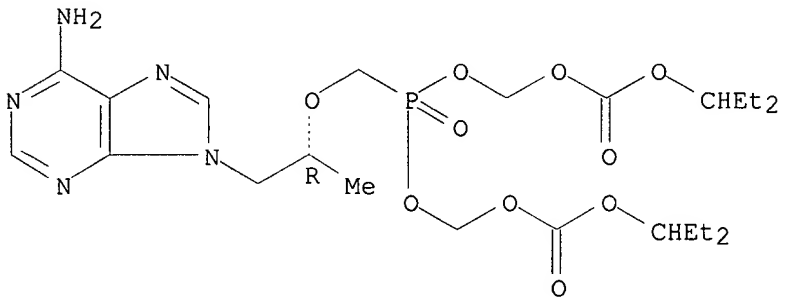
RN 201341-05-1 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 201341-07-3 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-ethylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 7 OF 7 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:762860 CAPLUS
DOCUMENT NUMBER: 128:97300

TITLE: Synthesis, in vitro biological evaluation and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) prodrugs

AUTHOR(S): Arimilli, M. N.; Kim, C. U.; Dougherty, J.; Mulato, A.; Oliyai, R.; Shaw, J. P.; Cundy, K. C.; Bischofberger, N.

CORPORATE SOURCE: Gilead Sci., Foster City, CA, 94404, USA

SOURCE: Antiviral Chem. Chemother. (1997), 8(6), 557-564
CODEN: ACCHEH; ISSN: 0956-3202

PUBLISHER: International Medical Press

DOCUMENT TYPE: Journal

LANGUAGE: English

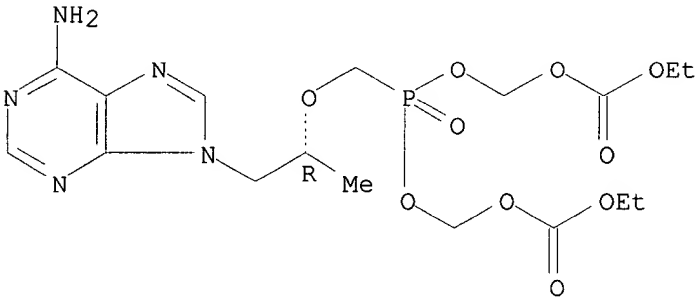
ABSTRACT:
Potentially orally bioavailable prodrugs of the antiretroviral agent 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) were evaluated. Alkyl Me carbamates were synthesized by alkylation of PMPA with the corresponding alkyl chloromethyl carbonate and N-alkyl chloromethyl carbamate reagents. The prodrugs were evaluated for in vitro antiviral activity in addn. to chem. and enzymic stability. The inhibition of human immunodeficiency virus type 1 (HIV-1) strain IIIB replication of MT-2 cells by the carbonate prodrugs was found to be 2.5-500-fold increased compared to PMPA. The alkyl Me carbonates, except t-Bu Me carbonate, had reasonable chem. stability at pH 2.2 and 7.4, but were rapidly converted to the corresponding monoester of PMPA in the presence of dog plasma. The alkyl Me carbamate prodrugs such a N-t-Bu Me carbamate were found to have high stability in vitro. Based on its chem. stability and good oral bioavailability, bis(POC)PMPA (iso-Pr methylcarbonate) was chosen as a clin. candidate.

IT **201340-95-6P 201340-97-8P 201340-99-0P**
201341-01-7P 201341-03-9P 201341-05-1P
201341-07-3P
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn., antiretroviral activity, and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine prodrugs)

RN 201340-95-6 CAPLUS

CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, diethyl ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

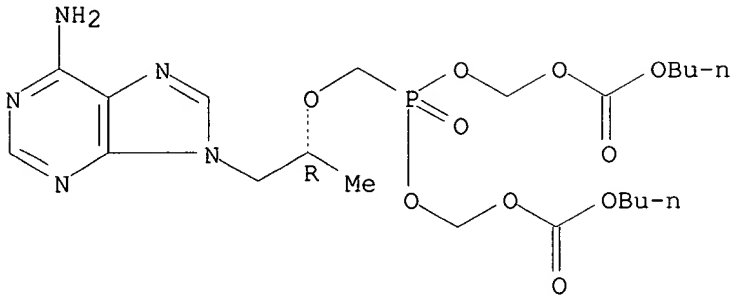
Absolute stereochemistry.



RN 201340-97-8 CAPLUS

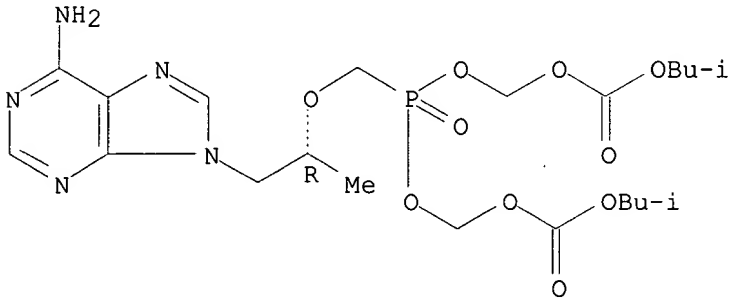
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, dibutyl ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



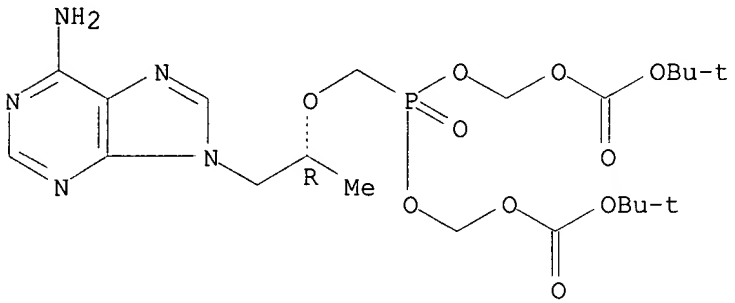
RN 201340-99-0 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(2-methylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



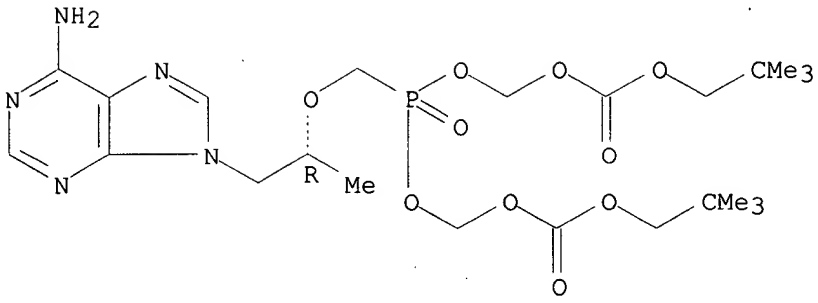
RN 201341-01-7 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1,1-dimethylethyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



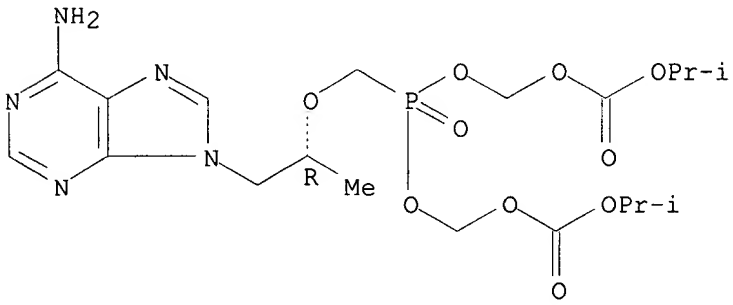
RN 201341-03-9 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(2,2-dimethylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



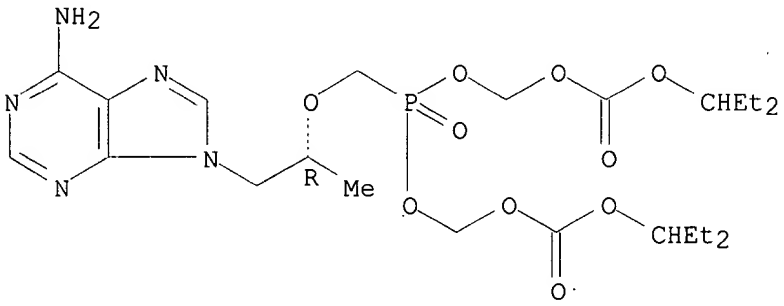
RN 201341-05-1 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 201341-07-3 CAPLUS
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-ethylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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SESSION WILL BE HELD FOR 60 MINUTES
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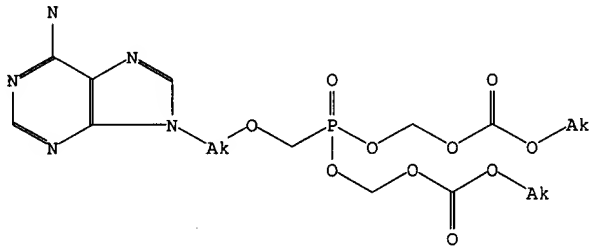

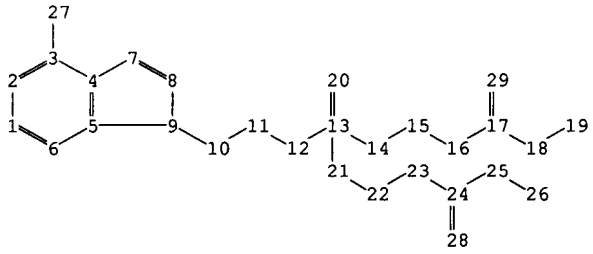

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28 29
ring nodes :
1 2 3 4 5 6 7 8 9
chain bonds :
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17-18 17-29 18-19 21-22 22-23 23-24 24-25 24-28 25-26
ring bonds :
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exact/norm bonds :
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exact bonds :
9-10 10-11 11-12 12-13 13-14 13-20 13-21 14-15 15-16 16-17
17-18 17-29 18-19 21-22 22-23 23-24 24-25 24-28 25-26
normalized bonds :
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Connectivity :
10:2EC 19:1EC 26:1EC
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom
10:CLASS 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom
18:Atom 19:CLASS 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom
26:CLASS 27:Atom 28:Atom 29:Atom